IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	: MARRIOTT et al.	Confirmation No: 3979
Appl. No.	: 09/646,111	
Filed	: November 20, 2000	
Title	: IMPROVED CRYSTAL STRUCTURE	
TC/A.U.	: 1615	
Examiner	: S. Tran	
Docket No.:	: MARR3001/REF	
Customer No:	: 23364	

BRIEF ON APPEAL

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

This brief on appeal is submitted in triplicate along with the required fee. A petition for a one month extension of time and the appropriate fee is submitted herewith extending the period for filing the brief to July 9, 2004. The brief is timely filed.

Any addition fees necessary for this appeal may be charged against the undersigned's Deposit Account No. 02-0200.

I. REAL PARTY IN INTEREST

The real party in interest is the Assignee of record, Glaxo Wellcome Inc.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences with respect to the claimed invention which will directly affect or be directly affected by or have a bearing on the

Board's decision in the pending appeal known to appellant, appellant's legal representative or assignee.

III. STATUS OF THE CLAIMS

This application contains 52 claims. Claims 1-41 have been canceled from this application.

Claims 42 through 52 are pending in the present application. Claims 42 through 49 and 52 are on appeal. Claims 50 and 51 are objected to as dependent on a rejected base claim but are said to contain allowable subject matter.

Claims 42 through 49 and 52 stand finally rejected under 35 U.S.C. 103 as prima facie obvious over prior art.

IV. STATUS OF AMENDMENTS AFTER FINAL REJECTION

An amendment was filed after final rejection. The amendment has been entered for purpose of appeal and obviates the rejection of claims 42-52 under 35 USC 112, second paragraph as this rejection has been withdrawn in the Advisory Action.

In addition, and as confirmed in a telephone conversation with Examiner Tran on July 7, 2004, the obviousness rejection of claims 42 to 49 and 52 over Hirao et al in view of Trofast et al. set forth in the Final Rejection has been withdrawn in the Advisory Action. The remaining two prior art rejections in the Final Rejection have been restated in the Advisory Action and these are the rejections on appeal and discussed in this brief.

V. SUMMARY OF INVENTION

The present invention relates to an improved process for producing crystals with controlled surface smoothness, size, shape and degree of crystallinity. It also relates to compositions comprising such crystals and to the use of certain crystals to produce improved pharmaceutical compositions (page 1, lines 4-7).

Surprisingly, applicants have found a process which allows crystals to be prepared without mechanical stirring or agitation during the period of crystallisation and crystal growth. The crystals so produced overcome the disadvantages of large variations in size and shape, and have improved surface smoothness and degree of crystallinity, and have an elongated shape. There are many fields in which such crystals would be of particular advantage, for example carrier and drug particles for use in inhaled pharmaceutical formulations (page 3, lines 25-31).

The present invention provides a crystallisation process comprising:

a) dissolving the substance to be crystallised in a medium wherein the viscosity of the medium can be adjusted.

b) applying a means for adjusting the viscosity of the medium until a gel with an apparent viscosity in the range 25 to 90 Pa.s at a shear rate of $1s^{-1}$ is reached;

c) allowing crystal growth;

d) applying a means for adjusting the viscosity of the medium until a fluid with an apparent viscosity less than 52 Pa.s at a shear rate of $1s^{-1}$ is reached; and

e) harvesting the crystals (page 4, lines 1-18).

The medium may be an aqueous solution of a polymer (page 4, lines 25 and 26). Preferably the polymer which comprises the medium is a Carbomer. Carbomers, a group of polyacrylic acid polymers cross-linked with either allylsucrose or allyl ethers of

pentaerythritol, provide a medium that meets the necessary criteria. (Page 8, lines 29-32).

Preferably the substance to be crystallised is a material suitable for used as a carrier or a drug in dry powder inhaler compositions. Especially preferred carriers are lactose and lactose monohydrate (page 7, lines 1-9).

In a further aspect, the present invention provides crystals obtainable by the process as hereinbefore described. The crystals are lactose, and preferably, the crystals are lactose monohydrate crystals (page 10, lines 20-23).

VI. ISSUES

One issue on appeal is whether a *prima facie* case of obviousness of the subject matter of claims 42-49 under 35 U.S.C. 103(a) over the teachings of Hirao et al in view Trofast et al and further in view of Douglas has been established.

The second issue on appeal is whether a prima facie case of obviousness has been established for the rejected subject matter of claim 52 under 35 U.S.C. 103(a) as being unpatentable over the teachings of Hirao et al. in view of Staniforth et al.

VII. GROUPING OF THE CLAIMS

The claims as grouped in the Final Rejection do not stand or fall together.

VIII. ARGUMENT

A. Statement of the Applicable Law

Applicants wish to direct the Examiner's attention to the basic requirements of a prima facie case of obviousness as set forth in the MPEP § 2143. This section states that to establish a prima facie case of obviousness, three basic criteria first must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

Section 2143.03 states that all claim limitations must be taught or suggested by the prior art. In re Royka, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." In re Wilson, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). If an independent claim is nonobvious under 35 U.S.C. 103, then any claim depending therefrom is nonobvious. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988).

Applicants also most respectfully direct the Examiner's attention to MPEP § 2144.08 (page 2100-114) wherein it is stated that Office personnel should consider all rebuttal argument and evidence presented by applicant and the citation of In re Soni for error in not considering evidence presented in the specification.

See also In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) for its holding that, "It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps".

A. Claims 42-49 are not prima facie obvious over the teachings of Hirao et al. in view of Trofast et al. and Douglas et al.

It is urged in the Advisory Action that Hirao teaches a process of shaping crystals of sugar alcohols by obtaining a saccharified starch solution with high maltose content, allowing crystallization and separating the crystallized solid. The viscosity of the solution can be regulated by the addition of water-soluble organic solvent, or elevated temperature. It is acknowledged that Hirao does not teach the viscosity of less than 25 Pas at a shear rate of $1s^{-1}$. However, it is further urged that no criticality is seen in the particular viscosity since Hirao obtains the same result desired by the applicant, e.g., a crystalline composition that is non-hygroscopic, free flowing, and can be any desired size or shape. It is then concluded that it would be obvious to one of ordinary skill in the art by routine experimentation, to determine a suitable viscosity of the solution to obtain the claimed invention. These statements are specifically traversed. Claims 42 and 46, the Independent claims on appeal, specify a crystallization process for lactose or lactose monohydrate. These are claim limitations which cannot be ignored.

Hirao on the contrary relates to anhydrous crystals of maltitol and the whole hydrogenated starch hydrolysate mixture solid containing these crystals and processes for the production and use thereof.

In the Summary of the Invention, at column 2 of Hirao, it is stated that the present inventors have investigated the properties of maltitol both to overcome these demerits (non-hygroscopic solid), and to obtain anhydrous crystals of maltitol and crystalline mixture solids, which have heretofore been regarded as unattainable.

As stated at column 2, beginning at line 52 of the patent, these efforts have resulted in the finding that maltitol crystals can be obtained as follows: A liquified starch solution with a low Dextrose Equivalent value is subjected to the enzymatic actions of isoamylase and β-amylase to obtain a saccharified starch solution with a high maltose

content, and the saccharified starch solution is then subjected to purification, concentration, crystallization and separation, obtaining a crystalline product with a maltose content of about 99% on dry solid basis. Thereafter, an aqueous solution of the product is hydrogenated in the presence of Raney nickel catalyst obtaining a maltitol solution with a high maltitol content up to about 98.5%. This in no way suggests the process of the claims on appeal which require dissolving lactose or lactose monohydrate in an aqueous solution of a Carbomer. As would be understood by one of ordinary skill in the art and as clearly defined in applicant's specification, a Carbomer, that is Carbomers, are a group of polyacrylic acid polymers cross-linked with either allylsucrose or allyl ethers of pentaerythritol as stated at the bottom of page 8 of applicants' specification. Again these are claim limitations of the claims on appeal which cannot be ignored and in no way suggested by the teachings of the Hirao reference.

Thus, there is no suggestion in the Hirao reference of the crystallization of lactose or lactose monohydrate, of dissolving the lactose or lactomonohydrates in an aqueous solution of a Carbomer, adjusting the viscosity in accordance with the claim limitations and precipitating lactose crystals having the desired properties. The specific statement that no criticality is seen in a particular viscosity since Hirao obtains the same results desired by applicant is traversed. Applicants' process relates to the preparation of lactose or lactose monohydrate crystals which may be used for inhalation therapy, for example, in a dry powder inhaler. The formation of the crystals is under controlled conditions as specified in the claims with respect to Carbomer and viscosities to arrive at the yield and necessary physical structure of the crystals as carrier particles. These are claimed limitations which cannot be ignored and distinguish the claimed process over the prior art.

In the Official Action it is acknowledge that Hirao does not teach that solid crystals can be used for inhalation. However, it is noted that Hirao in column 5, lines 20-58 teaches besides anhydrous crystals of maltitol, other sugar alcohols such as

sorbitol, maltotritol and maltotetraitol can be used for various uses, e.g., for foods, cosmetics and drugs. However it is clear from the further disclosure of the patent that the maltitol solid is used as a sweetener. Also as stated at the bottom of column 6 of the patent, they are favorably useable for reducing the carciogenicities of cosmetics and drugs, such as gargle and toothpaste by replacing sucrose therewith as well as for sweetening them as would be appreciated by one of ordinary skill in the art.

Additionally, in the paragraph bridging columns 7 and 8 of the patent, the anhydrous crystals of maltitol or crystalline mixture solid can be added freely to other substances such as vitamin, antibiotics or microorganisms prior to shaping in the admixture is then prepared into the desired shape for example, granule with a granulizer, or tablet with a tabletting machine. There is absolutely no suggestion that these can be used inhalation therapy.

This is especially true with respect to claim 48 which provides for pharmaceutical formulation for administration by inhalation comprising lactose monohydrate crystals as claimed in claim 47. Claim 49 provides a pharmaceutical formulation for administration by inhalation comprising lactose monohydrate crystals as claimed in claim 47 and/or fluticasone propionate or salmeterol xinafoate crystals. These claim limitations are not described in the combination of references relied upon in the rejection and further patentably distinguish the claimed subject matter over the prior art.

As clearly noted on page 5 of applicant's specification it has been found that medicaments for administration by inhalation should be of a control particle size in order to achieve maximum penetration into the lungs, preferably in the range of 1 to 10 micrometers in diameter. Unfortunately, powders in this particle size range, for example micronized powders, have a high bulk volume and have very poor flow characteristics due to the cohesive forces between the individual particles. These characteristics create handling and metering difficulties during manufacture of the medicament powder and most importantly, adversely effect the accurate dispensing of the powder within the

inhalation device. As stated at page 6 of applicant's specification, surprisingly the process of the present invention can be used to produce crystals of a drug or carrier with controlled size and shape, improved surface smoothness and degree of crystallinity and elongated shape. Such crystals overcome some of the formulation difficulties of compositions for inhalation.

In addition, the attention is directed to the comparative results contained in applicants' specification concerning the properties of the crystals prepared in accordance with the present invention as compared with prior art and clearly demonstrate the patentability of the presently claimed process and the product obtained thereby.

Claims 44 and 46 on appeal adjust the viscosity of the Carbomer by adjustment of the pH of the aqueous solution of the Carbomer. These are claim limitations which cannot be ignored and further patentably define over the prior art relied upon in the final rejection. The viscosity of Carbomer gel changes reversibly with the pH value of the solution. The viscosity reaches a maximum at pH 6-11 but is considerably reduced if the pH is less than 3 or greater than 12. Therefore, the crystallisation can be carried out in a neutralized Carbomer gel. After which the gel can be converted to a fluid by acidification such that the crystals may be readily harvested. These are process parameters of the claimed process which further patentably distinguish over the prior art.

Applicants most respectfully submit that the teachings of the secondary references do not overcome the deficiencies with the primary reference as discussed above and which clearly and unequivocally relate to a process of shaping anhydrous crystals of maltitol and uses thereof as a sweetener. In the Advisory Action it is urged that Trofast teaches a stable crystallinic form of fine-grained substance or substance mixed or useful for inhalation with specific reference to page 4, lines 23-30. This teaching is that the object of the present invention (the Trofast invention) is to provide

a reliable process for providing a stable crystallinic form to a fine-grained substance or a substance mixture, which can be produced, stored and used while maintaining the aerial dynamic properties required for inhalation of such a substance or substance mixture. The various processing steps are then set forth comprising steps a) to e). None of these processing steps remotely relate to those of the primary reference or the presently claimed process of the claims on appeal.

On page 6 of the Trofast reference, a general statement is made concerning doses and inhalation devices which utilize a carrier. Such a carrier may be carbohydrates including maltitol. It would be appreciated by one of ordinary skill in the art that this is just a very broad disclosure and not one of equivalents. The preference is for lactose or mannitol. The exemplification provided on pages 11-12 describe lactose as a carrier.

It is urged on page 3 of the advisory action that it would have been obvious for one of ordinary skill in the art to optimize the solid crystalline mixture of Hirao as a carrier used for inhalation of pharmaceutical formulation in the teaching of Trofast, because the references teach the advantageous result of the use of carrier, such as maltitol and lactose monohydrate as a carrier for inhalation formulation. This statement is specifically traversed. At most, the combination of the two references would lead one of ordinary skill in the art to the use of maltitol as a carrier and not lactose or lactose monohydrate. It does not suggest substituting lactose or lactose monohydrate into the process of Hirao et al. to arrive at the presently claimed process as would be appreciated by one of ordinary skill in the art. There is no motivation to make the necessary combination, absent Applicants' teaching, which would be impermissible hindsight. In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.).

The deficiencies of the Hirao and Trofast et al. references as discussed above are not overcome by the teachings of the Douglas patent. It is noted at the bottom of

page 3 of the Advisory Action that the Carbomer is a well known starch or thickener or binder in the pharmaceutical art. This statement is specifically traversed. It is noted on page 8 of applicant's specification Carbomers are a group of polyacrylic acid polymers cross-linked with either allylsucrose or allyl ethers pentaerythritol and there is no suggestion that these are well known starches. Clarification concerning the statement that Carbomer is a well known starch is most respectfully requested in the Examiner's Answer should this argument be pursued.

Applicants agree that the Douglas et al. reference teaches an oral administration composition which is substantially free of bitter taste. Specific reference in the Advisory Action is made to column 7 of the patent wherein it is stated that aqueous suspensions may be obtained by dispersing the lipid coated particles in an aqueous vehicle. Suitable vehicles include sucrose syrup; hydrogenated sucrose syrup, sorbitol solution and concentrated solutions of other sugars; aqueous solutions thickened with cellulose based polymers such as hydroxypropylmethyl cellulose, methyl cellulose or microcrystalline cellulose in suspension; aqueous solutions thickened with polysaccharides such as starch, aqueous solutions thickened with polyacrylates such as carbopol and aqueous solutions thickened with colloidal dispersing agents such as magnesium aluminum silicate. This in no way would lead one of ordinary skill in the art to substituting carbopol for a liquified starch in Hirao.

As noted at column 2, line 52 of the Hirao patent, a liquified starch solution with a low Dextrose Equivalent value is subjected to enzymatic actions of isoamylase and β-amylase to obtain a saccharified starch solution with a high maltose content. Clearly one of ordinary skill in the art would not substitute carbopol for the starch as urged in the Advisory Action. This is clearly evidence of hindsight and the only motivation provided is in applicants' specification which cannot be used as a teaching reference. The rejection is clearly based on impermissible hindsight reconstruction of the claims on appeal by selecting features from the prior art, based on Applicants' teaching. The necessary motivation to arrive at the claims on appeal is not found in the prior art.

Accordingly, it is most respectfully submitted that a *prima facie* case of obviousness has not been established and the rejection should be reversed.

B. Claim 52 is not prima facie obvious under 35 U.S.C. 103(a) over the teachings of Hirao et al. in view of Staniforth et al.

A *prima facie* case of obviousness has not been established for the lactose monohydrate subject matter of claim 52 which is held to be unpatentable over Hirao et al. in view of Staniforth. Clearly, this rejection should be reversed.

For the reasons discussed above, Hirao et al. in no way suggests the subject matter of lactose monohydrate having an elongation ratio of from 1.55-2.20 prepared in accordance with the process of claim 47 which is dependent upon claim 42.

It is urged that Staniforth teaches carrier particles useful in dry powder inhalers comprising one or more crystalline sugars including lactose (but not lactose monohydrate, a claim limitation), having particle diameters between from 60 μm to 180 μm. Staniforth teaches at page 10 the carrier particles are particles of lactose and the carrier particles have a diameter which lies between 20 μm and 1000 μm and more preferably 50 μm and 1000 μm. It is then concluded in the Advisory Action that it would have been obvious for one of ordinary skill in this art to modify Hirao crystalline solid carrier to have the particle size suitable for inhalation in view of the teaching of Staniforth, because the references teach the advantageous results and the crystalline sugars in the pharmaceutical art.

As previously pointed out by Applicants, even if one were to modify the Hirao crystalline solid carrier as suggested in the Official Action, this would result in a maltitol carrier, for use as sweetener, and not the lactose monohydrate in accordance with the present invention. This is particularly true in view of the evidence contained in

applicants' specification which must be taken into consideration. The necessary motivation to modify the reference in the expectation of obtaining the lactose monohydrate is not contained in the combination of references and Applicants' specification may not be relied upon as a teaching reference. Again, see In re Fritch, 23 USPQ 1780, 1784(Fed Cir. 1992) ("It is impermissible to engage in hindsight reconstruction of the claimed invention, using the applicant's structure as a template and selecting elements from references to fill the gaps.). Accordingly, it is most respectfully requested that this rejection be reversed.

IX. CONCLUSION

In view of the above arguments, the rejections of the claims on appeal should not be sustained. The prior art rejections should be reversed and the application passed to issue.

Respectfully submitted,

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APPENDIX

CLAIMS ON APPEAL

42. A crystallisation process for lactose or lactose monohydrate comprising:

a) dissolving lactose or lactose monohydrate in an aqueous solution of a Carbomer;

b) applying a means for adjusting the viscosity of the aqueous solution of a Carbomer until a gel with an apparent viscosity in the range 25 to 90 Pa.s at a shear rate of $1s^{-1}$ is reached;

c) allowing crystal growth;

d) applying a means for adjusting the viscosity of the aqueous solution of a Carbomer until a fluid with an apparent viscosity less than 25 Pa.s at a shear rate of $1s^{-1}$ is reached; and

e) harvesting the crystals.

43. A crystallisation process as claimed in claim 42, wherein the means for adjusting the viscosity of the aqueous solution of a Carbomer is temperature change, ultrasound, thixotropicity, electro-rheology, mechanical shear, chemical additive, or pH change.

44. A crystallisation process as claimed in claim 43, wherein the means for adjusting the viscosity of the aqueous solution of a Carbomer is pH change.

45. A crystallisation process as claimed in claim 42, wherein the crystals are harvested by means of collection by filtration.

46. A crystallisation process as claimed in claim 42, wherein the process comprises:

a) dissolving lactose or lactose monohydrate to be crystallised in an aqueous solution of a Carbomer wherein the viscosity of the medium is pH-dependent;

b) adjusting the pH of the aqueous solution of a Carbomer until a gel with an apparent viscosity in the range 25 to 90 Pa.s at a shear rate of $1s^{-1}$ is reached;

c) allowing crystal growth;

d) adjusting the pH of the aqueous solution of a Carbomer until a fluid with an apparent viscosity less than 25 Pa.s at a shear rate of $1s^{-1}$ is reached; and

e) harvesting the crystals.

47. Lactose monohydrate crystals obtained according to the process as claimed in claim 42.

48. A pharmaceutical formulation for administration by inhalation comprising lactose monohydrate crystals as claimed in claim 47.

49. A pharmaceutical formulation for administration by inhalation comprising lactose monohydrate crystals as claimed in claim 47 and/or fluticasone propionate or salmeterol xinafoate crystals.

50. A crystallisation process as claimed in claim 42, wherein the crystallised lactose monohydrate has an elongation ratio of 1.58 ± 0.33 and a size in the range of 63 to 90 μm.

51. A lactose monohydrate according to claim 47, having an elongation ratio 1.58 ± 0.33 and a size in the range of 63 to 90 μm.

52. Lactose monohydrate according to claim 47, having an elongation ratio of from 1.55 -2.20.